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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/665,493	09/20/2000	William C. Manning JR.	PP01588.005 (20263-40)	1563

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EXAMINER	
TON, THAIAN N	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 03/04/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/665,493	MANNING ET AL.	
	Examiner	Art Unit	
	Thai-An N Ton	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 December 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-28 and 30-44* is/are pending in the application.

4a) Of the above claim(s) *1-16,23-25 and 30-44* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *17-22 and 26-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *11/18/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicants' Amendment, filed 12/19/03, has been entered. Claims 1-28, 30-44 are pending. Claims 1-16, 23-25 and 30-44 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 14. Claims 17-22 and 26-28 have been amended and are under current examination.

Priority

The priority should be updated to reflect that U.S. Patent No. 09/525,956 is now abandoned. See p. 1, line 5 of the specification.

Specification

The disclosure is objected to because of the following informalities:

p. 8, line 4 of the specification does not have a SEQ ID NO.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The prior rejection of claims 17-21 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of inhibiting neovascularization in the eye, comprising the intraocular co-administration of an AAV-vector which directs the expression of VEGF and an AAV-vector which directs the expression of soluble Flt-1, wherein the simultaneous administration of the vectors inhibits neovascularization in the eye, the specification does not reasonably provide enablement for methods of inhibiting angiogenesis in a diseased eye of a subject comprising administering intraocularly a gene delivery vector which directs the expression of an anti-angiogenic factor, such that administration of said vector inhibits neovascularization of the diseased eye. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Applicants argue that as amended, an aspect of the claimed invention recites methods of inhibiting angiogenic factors of neovascular diseases in the eye and that the present invention simulated subretinal and choroidal neovascularization by (1) injection of angiogenic transgene; (2) optic nervice (ON) crush; (3) increase in intraocular pressure. Further, Applicants point to Lip et al. (2002) who describe that levels of VEGF are elevated in patients with normal tension glaucoma and primary open glaucoma." Applicants conclude that retinal tissue damage stimulates angiogenic factors as seen by an increase level of VEGF. Further,

Applicants cite Lip and Kendall (1994) to provide teachings that soluble FLT-1 levels are significantly lower in patients with normal tension glaucoma and primary open angle glaucoma and that sFLT-1 has angiostatic or anti-angiogenesis properties by way of its antagonist activity against VEGF by binding to VEGF. Applicants thus argue that damage to the optic nerve by ON crush, or an increase in an intraocular pressure, as performed in the instant invention, and inhibiting angiogenesis or neovascularization by the co-administration of AAV-vectors which express anti-angiogenic factors provide a good model to show the inhibition of neovascularization. See pp. 8-9 of Applicants' Response.

Neither Lip *et al.* nor Kendall *et al.* have been provided, and thus cannot be considered with regard to Applicants' arguments. Applicants' arguments are not found to be persuasive. The specification teaches 1) that subretinal injections of AAV-VEGF in a rat produced subretinal and choroidal neovascularization [Example 16], and that 2) the co-injection of rAAV-sFLT-1 with the rAAV-VEGF vector in the subretinal space showed functional rescue when compared to animals which only received an injection of rAAV-VEGF [Example 17]. Thus, it is reiterated that the claims require that the eye of the subject be diseased prior to administration of the vector that directs the expression of an anti-angiogenic factors, in the instant case, sFLT-1, in order to show inhibition of neovascularization in a diseased eye.

The specification fails to provide teachings wherein the rat model has developed a neovascular disease prior to administration of sFLT-1, such that the

expression of the sFLT-1 vector would inhibit neovascularization. However, the model never develops neovascular disease prior to Flt-1 vector administration. If the model never develops neovascular disease, then it is not seen as how the model is a representation of all forms of "inhibiting". The specification fails to provide teachings or guidance as to how to correlate the results presented in the specification with the inhibition of ongoing neovascular disease in a patient. For example, there are no teachings or guidance provided by the specification with regard to which individuals would be at risk for developing neovascular disease, such that the disease could be inhibited prior to the onset, or at what stage of neovascular disease onset the administration of Flt-1 would need to occur in order to prevent neovascular disease. The specific guidance is to inhibiting the onset of neovascular disease by inhibition of angiogenesis prior to the occurrence of angiogenesis. Note that inhibition is a form of treatment of neovascular disease. As such, the example provided by the specification, wherein co-injection of the two described vectors inhibits the formation of neovascular disease in the eye, does not provide a correlation with inhibition of neovascular disease in an individual who may potentially develop the disease, not in an individual who has experienced neovascularization. The specification provides no teachings or guidance to show that injection of the sFlt-1 vector to the rat model that already exhibits neovascularization in the eye would show a functional rescue. The specification teaches that inhibition is to result in the functional rescue of the eye. However, the

model as taught by the specification cannot correlate with functional rescue of the eye, as no eye function is ever lost in the rat model. This exemplified inhibition is not representative of treatment or inhibition in a patient who develops neovascularization in the eye *de novo*, prior to detection, and the administration of sFlt-1 post-neovascularization. Note that Applicants' amendment to the claims, with regard to the recitation of "a diseased eye of a subject" is read in light of the specification, which is directed to diseases of neovascularization in the eye. As such, a diseased eye in a subject is properly interpreted as one where neovascularization has occurred.

Applicants argue that with regard to the enablement of gene therapy, the claimed invention is supported by the specification, in that co-administration of anti-angiogenic factors to a damaged eye, inhibits angiogenesis, as shown by the working examples of the specification. See p. 9, last ¶ of Applicants' Response. Applicants argue that therefore, the specification enables one skilled in the art to administer AAV-vectors to tissue-damaged regions of the eye resulting in the inhibition of neovascularization. Applicants argue that the cite art of Ali addresses issues when using AAV vectors including lack of high titers and contamination of wild-type AV. Applicants argue that these problems are addressed in the present invention in the examples, because high titers are achieved and wild-type contamination is not an issue in the present invention. See p. 10 of Applicants' Response.

This is not found to be persuasive. Note that the claims have found to be enabled for the inhibition of neovascularization in the eye, comprising the intraocular co-administration of an AAV-vector which directs the expression of VEGF and an AAV-vector that directs the expression of soluble Flt-1, wherein the simultaneous administration of the vectors inhibits neovascularization in the eye. The enabled scope of the claims is based upon the lack of guidance or teachings provided by the specification with regard to the inhibition of angiogenesis in a diseased eye, as stated previously, as well as upon the state of the art of gene therapy. The prior cited art of Romano and Ali are provided to show that gene therapy, as a broad-based art, is unpredictable. Therefore, specific vectors, methods of administration, and a therapeutic effect must be correlative to what is claimed. In the instant application, a correlation cannot be drawn for the reasons discussed in the prior Office action. As established by the state of the art of gene therapy, note that therapeutic expression is not an inherent feature in methods of either *in vivo* or *ex vivo* gene transfer involving expression of a protein of interest. In fact, the lack of a therapeutic response in many gene therapy protocols attests to the unpredictable and undeveloped status of the art of gene therapy. The lack of correlative teachings in the art at the time of filing for gene therapy, as a whole, makes it incumbent upon the specification to provide guidance that leads to a therapeutic outcome.

In the instant specification, while the intraocular co-administration of rAAV-VEGF and rAAV-sFlt-1 inhibited the formation of neovascular disease, there is no correlation between the observed results and the inhibition of neovascularization in a diseased eye by the administration of a gene delivery vector that directs the expression of an anti-angiogenic factor. As discussed previously, the specification only provides support for the co-administration of the described vectors, and further, the specification fails to provide guidance or teachings with regard to which individuals would be at risk to development of neovascular diseases of the eye, such that one could inhibit the formation of the disease.

Accordingly, in view of the lack of guidance or teachings provided by the specification with regard to inhibition of neovascular disease by administration of soluble Flt-1, as well as the unpredictable and undeveloped state of the art with respect to the gene therapy art, as well as to the art of gene therapy of the eye, it would have required undue experimentation for one skilled in the art to make and/or use the claimed vectors and methods of using the same.

Claim Rejections - 35 USC § 102

The prior rejection of claims 22 and 26 under 35 U.S.C. §102 is withdrawn in view of Applicants' amendment to the claims reciting, "A retroviral gene delivery vector ...".

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The prior rejection of claims 22, 27-28 under 35 U.S.C. 103(a) as being unpatentable over Kendall *et al.* when taken with Bujard *et al.* is maintained for reasons of record.

Kendall *et al.* teach the isolation and cloning of the anti-angiogenic factor, soluble FLT (see p. 10705, 2nd column). Kendall *et al.* differ from the claimed invention in that they do not disclose cloning soluble FLT into a retroviral vector generated from either HIV or FIV. However, prior to the time of filing, Bujard *et al.* teach the construction of vectors that can be used to regulate gene expression. Bujard *et al.* teach that these vectors can be derived from a virus, such as replication defective retroviruses or adeno-associated viruses (see col. 12-13, bridging paragraph). Further, Bujard *et al.* teach that a gene that can be expressed using the described vector can be soluble receptors, such as soluble TNF receptor (see col. 37, lines 6-16).

Applicants argue that the claimed invention is not obvious over the prior art because they do not teach all of the claimed limitations. Particularly, Applicants

argue that, "At best, when one skilled in the art combines the references of Kendall *et al.* and Bujard *et al.*, the result is a recombinant retroviral vector containing the heterologous sequence of sFLT-1. However, this recombinant retroviral vector does not inhibit neovascularization of the diseased eye." See pp. 13-14 of Applicants' Response.

In response, it is noted that the claims as amended recite that administration of the gene delivery vector inhibits neovascularization of a diseased mammal [see claim 22]. This limitation is an intended use of the product and does not narrow the scope of the product over the prior art. MPEP §2111.02 states, .. "[I]n apparatus, article, and composition claims, intended use must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art." *In re Casey*, 152 USPQ 235 (CCPA 1967); *In re Otto*, 136, USPQ 458, 459 (CCPA 1963). It is further noted that, "Where the claimed and prior art products are identical or substantially identical in structure or compositions, or are produced by identical or substantially identical processes, a *prima facie* case of either anticipation **or obviousness** has been established. MPEP 2112.01 states:

> In re Best, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." In re Spada, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). Therefore, the prima facie case can be rebutted by evidence showing that the prior art products do not necessarily possess the characteristics of the claimed product. In

re Best, 562 F.2d at 1255, 195 USPQ at 433. See also Titanium Metals Corp. v. Banner, 778 F.2d 775, 227 USPQ 773 (Fed. Cir. 1985).

Furthermore, reliance upon inherency is not improper even though a rejection is based on Section 103 instead of 102. *In re Skoner,* 517 F.2d 947, 186 USPQ 80 (CCPA 1975).

Accordingly, in view of the teachings of Bujard *et al.*, it would have been obvious for one of ordinary skill in the art, at the time the claimed invention was made, to use clone the soluble FLT described by Kendall *et al.* into the vectors described by Bujard *et al.* with a reasonable expectation of success. One of ordinary skill in the art would have been sufficiently motivated to make such a modification as the vectors described by Bujard *et al.* could more efficiently transfect cells *in vivo* to examine gene function.

Thus the claimed invention as a whole was clearly *prima facie* obvious at the time the claimed invention was made especially in the absence of sufficient, clear and convincing evidence to the contrary.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Thaian N. Ton whose telephone number is (571) 272-0736. The Examiner can normally be reached on Monday through Friday from 8:00 to 5:00 (Eastern Standard Time), with alternating Fridays off. Should the Examiner be unavailable, inquiries should be directed to Amy Nelson, Acting SPE of Art Unit 1632, at (571) 272-0804. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 872-9306.

TNT

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